Journal of Cardiology 67 (2016) 98–103

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Prognostic significance of changes in cystatin C during treatment of acute cardiac decompensation

Hideaki Inazumi (MD)*, Satoshi Koyama (MD), Yohei Tanada (MD), Hisayoshi Fujiwara (MD, PhD, FJCC), Yoshiki Takatsu (MD, PhD), Yukihito Sato (MD, PhD, FJCC)

Department of Cardiovascular Medicine, Hyogo Prefectural Amagasaki Hospital, Amagasaki, Hyogo, Japan

ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 20 March 2015
Accepted 17 April 2015
Available online 15 June 2015

Keywords:
Cystatin C
Heart failure
Cardiac decompensation
Worsening renal function

ABSTRACT

Background: The long-term prognostic significance of in-hospital worsening renal function (WRF) during treatment of acute cardiac decompensation (ACD) remains controversial.
Methods: We analyzed data from 100 patients (mean age = 75 years; 53% men) presenting with ACD, in whom the serum cystatin C (Cys-C) concentration was measured upon admission to the hospital and 4 days later. We examined the relationship between changes in Cys-C and primary study endpoint of risk of death and re-hospitalization for management of ACD, up to 180 days, searched for predictors by multiple variable analysis and calculated the hazard ratios (HR) and 95% confidence intervals (CI).
Results: A median (25th to 75th percentile) increase in Cys-C from 1.29 (0.88–1.66) mg/l on day 1 to 1.31 (1.00–1.84) mg/l on day 4, observed in 66% of all patients, was associated with a significant decrease ($p = 0.040$) in the 180-day incidence of primary study endpoint. By multiple variable regression analysis, an increase in Cys-C was an independent predictor of death and re-hospitalization for management of ACD (HR 0.415; 95% CI 0.193–0.885; $p = 0.023$).
Conclusions: An increase in serum Cys-C concentration after hospitalization for management of ACD was associated with a decreased, long-term incidence of primary study endpoint.

Introduction

Acute cardiac decompensation (ACD) is the most frequent cause of hospitalization in the Western world [1,2]. Its pathophysiology is being abundantly studied with a view to lower the high re-hospitalization rates and mortality associated with it. The pathologic interaction between heart and kidney, also known as cardio-renal syndrome, is one of the greatest therapeutic challenges [3,4]. Worsening renal function (WRF), defined as a >0.3 mg/dl increase in serum creatinine concentration, occurs in approximately 25% of patients admitted to hospital for management of ACD [5,6]. Although the mechanisms of WRF have not been completely clarified, a low cardiac output, elevation of the central blood pressure, renin–aldosterone–angiotensin axis dysfunction, sympathetic hyperactivity, oxidative injury, and a reduced renal perfusion are important contributing factors [4]. In previous studies, WRF has been associated with a high mortality and re-hospitalization rate [5,7]. However, several recent studies are conflicting with this observation and the prognostic value of in-hospital WRF remains contentious [8–14].

Although various markers have been identified as potential contributors to the cardio-renal syndrome in the past decade, nearly all studies have defined in-hospital WRF as a rise in serum creatinine or in estimated glomerular filtration rate (eGFR) calculated from it. Cystatin-C (Cys-C) is a recently described marker of renal function [16,17]. Its serum concentration is not modified by age, gender, race, or muscle mass, and changes in eGFR could be more accurately and rapidly detected with Cys-C than with creatinine [18,19]. Cys-C is also a better predictor of mortality and adverse cardiovascular events than serum creatinine-based estimates in acute and chronic heart failure [20–23]. However, the changes in Cys-C during hospitalization for ACD and its prognostic contribution have rarely been reported and are controversial [24–26]. This observational study examined the changes in Cys-C during treatment of ACD, its associations with other factors, and its prognostic contribution in patients presenting with ACD.

* Corresponding author at: Department of Cardiovascular Medicine, Hyogo Prefectural Amagasaki Hospital, 1-1-1 Higashidaimotsu, Amagasaki, Hyogo 660-0828, Japan. Tel.: +81 78 6482 1521; fax: +81 78 6482 7430.
E-mail address: i_hide_aki@yahoo.co.jp (H. Inazumi).

http://dx.doi.org/10.1016/j.jjcc.2015.04.014
0914-5087/

Materials and methods

We studied 100 Japanese patients admitted to our hospital between February 2009 and March 2012 for management of ACD diagnosed based on the typical symptoms and signs such as dyspnea at rest or minimal effort with signs of pulmonary and/or peripheral congestion, chest radiograph, 12-lead electrocardiogram (ECG), laboratory tests, echocardiography, and according to current guidelines [27]. During hospitalization, the patients were treated with a vasodilator and a diuretic, with or without inotrope, as necessary. Patients presenting with (a) an acute myocardial infarction, (b) shock, defined as hypotension requiring continuous infusions of norepinephrine, (c) an overt infection, (d) a serum creatinine concentration >3 mg/dl, or (e) a need for hemodialysis or a mechanical cardiac assist device or mechanical ventilator were excluded from this study. We also excluded the patients who died during the initial hospitalization, who underwent a cardiac operation during the initial hospitalization or during the follow-up, or whose follow-up data were not available (Fig. 1). The present study was approved by the Ethical Committee of Hyogo Prefectural Amagasaki Hospital and conducted in compliance with the Declaration of Helsinki.

Study measurements

After verification of the patients' medical histories and drug regimens, blood samples were obtained within 6 h and 4 days after their admission to the hospital, and analyzed for serum hemoglobin, albumin, bilirubin, blood urea nitrogen (BUN), creatinine, Cys-C, electrolytes, and N-terminal pro B-type natriuretic peptide. Cys-C was measured, using the latex agglutination-turbidimetric immunoassay (IATRO Cys-C; Mitsubishi Chemical Medicine Corporation, Tokyo, Japan), with a cut-off value of 1.0 mg/l. As a categorical variable, according to the change in Cys-C, the patients were divided between a group in whom the Cys-C serum concentration (a) increased between day 1 and day 4 ($Cys_{DAY\ 4\ >\ DAY\ 1}$) and (b) the Cys-C serum concentration decreased or remained unchanged between day 1 and day 4 ($Cys_{DAY\ 4\ \leq\ DAY\ 1}$). Similarly, they were divided between a group in whom (a) eGFR increased or remained unchanged between day 1 and day 4 ($eGFR_{DAY\ 4\ \geq\ DAY\ 1}$) and (b) eGFR decreased between day 1 and day 4 ($eGFR_{DAY\ 4\ <\ DAY\ 1}$).

The primary endpoint of the study was a composite of (a) deaths from all causes and (b) unplanned re-hospitalizations for management of ACD.

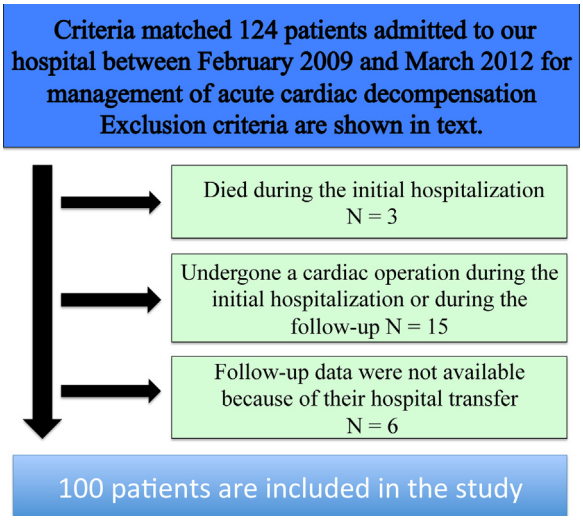

Fig. 1. Study flow chart.

Statistical analysis

The categorical variables are expressed as counts and percentages and the normally distributed continuous variables as means ± standard deviation (SD). Because body mass index and the serum concentrations of bilirubin, creatinine, Cys-C, and N-terminal pro B-type natriuretic peptide were not normally distributed, they were log-transformed for the analysis, and are expressed as medians (25th to 75th percentiles). Differences in serum Cys-C concentrations between day 1 and day 4 were examined by Wilcoxon signed-rank test. Differences in clinical and laboratory measurements between baseline and day 4 in patients with $Cys_{DAY\ 4\ >\ DAY\ 1}$ and patients with $Cys_{DAY\ 4\ \leq\ DAY\ 1}$ were tested by Fisher's exact test for categorical variables and Student's *t*-test or Wilcoxon rank sum test, for continuous variables, as appropriate.

Kaplan–Meier curves were constructed to examine the effect of changes in Cys-C and eGFR on the adverse event-free survival, and the differences in survival rates were tested by log-rank test. We also examined by Cox proportional hazard regression analysis whether the association between changes in Cys-C and event-free survival influenced the outcome of ACD independently from other variables. Variables that emerged with a *p*-value <0.10 by single variable analysis, including systolic blood pressure, and sodium, potassium, bilirubin, inotrope use, and $Cys_{DAY\ 4\ >\ DAY\ 1}$ concentrations besides age and gender, were entered in a multiple variable regression analysis. To ascertain the effect of baseline renal function on the change in Cys-C concentration, we added the concentration of Cys-C on admission to the hospital in the analysis. All analyses were two-sided, with $p < 0.05$ considered statistically significant. The analyses were performed with the JMP®, version 10.0 software (SAS Corporation, Cary, NC, USA).

Results

Baseline patient characteristics

We enrolled 100 patients who met the inclusion criteria and whose characteristics are shown in Table 1. Their average age was 75 years and 53% were men.

Changes in renal function during the treatment period

The median serum Cys-C concentration increased from 1.29 (0.88–1.66) mg/l on day 1, to 1.31 (1.00–1.84) mg/l on day 4 ($p < 0.001$; Fig. 2). Between day 1 and day 4, the mean BUN increased from 24 ± 11 mg/l g/dl to 25 ± 11 mg/l g/dl, and mean eGFR decreased from 50 ± 22 ml/min/1.73 m^2 to 49 ± 22 ml/min/1.73 m^2, although neither change was statistically significant.

Baseline characteristics of patients whose Cys-C serum concentration increased during treatment

The Cys-C concentration increased during treatment of ACD in 66 patients, from 1.09 (0.82–1.56) mg/l on day 1 to 1.25 (0.96–1.78) mg/l on day 4. Their baseline characteristics are compared with those of the patients whose Cys-C concentration did not increase in Table 1. Patients in the $Cys_{DAY\ 4\ >\ DAY\ 1}$ group had a higher prevalence of atrial fibrillation, a lower left ventricular ejection fraction and higher heart rate, and were less often treated with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or a loop diuretic on admission to the hospital. They also had lower creatinine, BUN, and Cys-C serum concentrations.

Table 1
Baseline characteristics of patients grouped according to change in cystatin C.

	Total (100)	$Cys_{DAY\ 4 > DAY\ 1}$ (66)	$Cys_{DAY\ 4 \leq DAY\ 1}$ C (34)	*p*
Age, years	75 ± 11	74 ± 11	76 ± 11	0.563
Women, *n*	47 (47)	33 (50)	14 (41)	0.526
Concomitant disorders				
Ischemic heart disease, *n*	37 (37)	23 (35)	14 (41)	0.662
Atrial fibrillation, *n*	252 (52)	29 (44)	23 (68)	0.034
Diabetes mellitus, *n*	34 (34)	24 (36)	10 (29)	0.514
Hypertension, *n*	78 (78)	49 (74)	29 (85)	0.308
Previous history of acute cardiac decompensation hospitalization, *n*	49 (49)	27 (41)	22 (65)	0.034
Drug therapy on admission				
Angiotensin-converting enzyme inhibitor or receptor blocker, *n*	51 (51)	28 (42)	23 (68)	0.021
Beta-adrenergic blocker, *n*	41 (41)	23 (35)	18 (53)	0.091
Loop diuretic, *n*	63 (63)	35 (53)	28 (82)	0.005
Aldosterone blocker, *n*	24 (24)	15 (23)	9 (26)	0.805
Left ventricular ejection fraction, %	50 ± 17	47 ± 17	55 ± 17	0.023
Body mass index, kg/m^2	24 ± 4.7	23 ± 4.6	25 ± 4.9	0.135
Heart rate, bpm	82 ± 22	86 ± 22	75 ± 19	0.009
Blood pressure, mmHg				
Systolic	139 ± 26	139 ± 26	136 ± 24	0.639
Diastolic	79 ± 18	81 ± 20	75 ± 13	0.208
Hemoglobin, g/dl	11 ± 2	11 ± 2.2	11 ± 1.7	0.836
Albumin, g/dl	3.6 ± 0.4	3.5 ± 0.5	3.6 ± 0.4	0.672
Blood urea nitrogen, g/dl	24 ± 11	22 ± 11	27 ± 11	0.007
Creatinine, mg/dl	1 [0.8–1.4]	1 [0.7–1.3]	1.2 [0.975–1.5]	0.013
Estimated glomerular filtration rate, $ml/min/1.73\,m^2$	50 ± 22	53 ± 22	45 ± 20	0.045
Cystatin C, mg/l	1.3 [0.9–1.7]	1.1 [0.8–1.6]	1.5 [1.2–1.9]	0.002
Sodium, mEquiv./l	140 ± 4.1	140 ± 4.1	140 ± 4.1	0.977
Potassium, mEquiv./l	4.0 ± 0.6	4.0 ± 0.6	4.0 ± 0.6	0.662
Bilirubin, mg/dl	0.7 [0.6–1.1]	0.7 [0.6–1.0]	0.8 [0.7–1.3]	0.285
N-terminal pro brain natriuretic peptide, pg/ml	3118 [1723–8166]	4097 [1743–9490]	2709 [1716–6626]	0.322
Inotropes use, yes	25 (25)	16 (24)	9 (26)	0.812

Values are means ± SD, numbers (%) of observations or medians [ranges].
Associations were tested by Wilcoxon rank sum tests or Fisher's exact tests as appropriate.
Cys, cystatin C.

Survival analysis

Over 180 days of follow-up, 4 patients died and 26 were re-hospitalized for management of ACD. The incidence of primary study endpoint was lower in the $Cys_{DAY\ 4 > DAY\ 1}$ than in the $Cys_{DAY\ 4 \leq DAY\ 1}$ group ($p = 0.040$; Fig. 3A), although it was similar in patients with $eGFR_{DAY\ 4 < DAY\ 1}$ and patients with $eGFR_{DAY\ 4 \geq DAY\ 1}$ ($p = 0.541$, Fig. 3B). By single variable Cox regression analysis, high systolic and diastolic blood pressures, high sodium and potassium, and low bilirubin concentrations at baseline, and (a) increase in Cys-C concentration and the absence of (b) inotrope use during treatment were associated with low rates of primary study

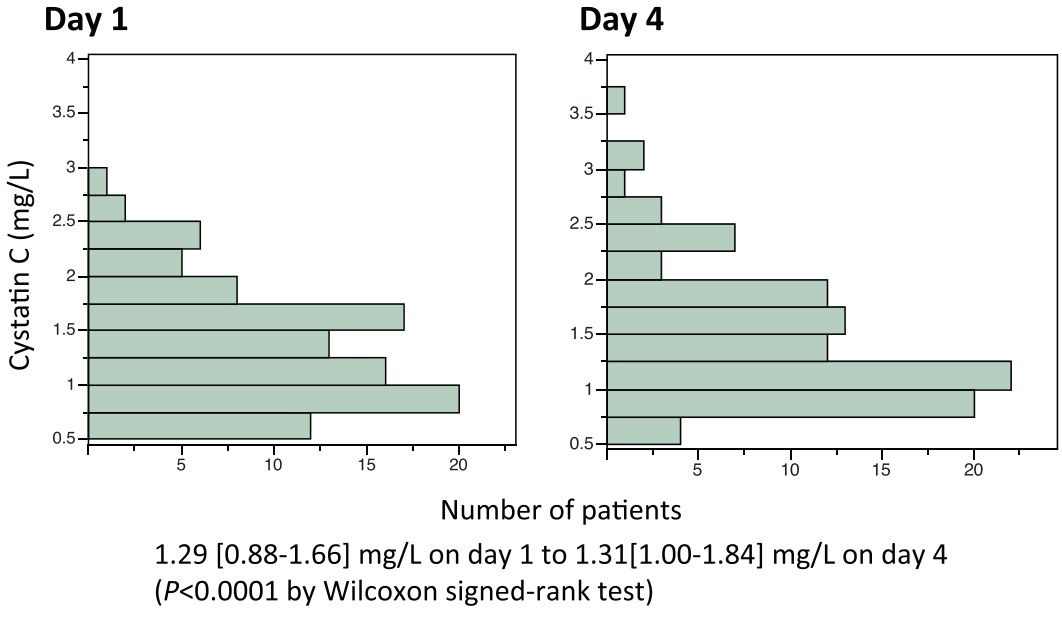

Fig. 2. Changes in cystatin C between day 1 and day 4. Comparisons of cystatin C were made by Wilcoxon signed-rank test ($p < 0.0001$).

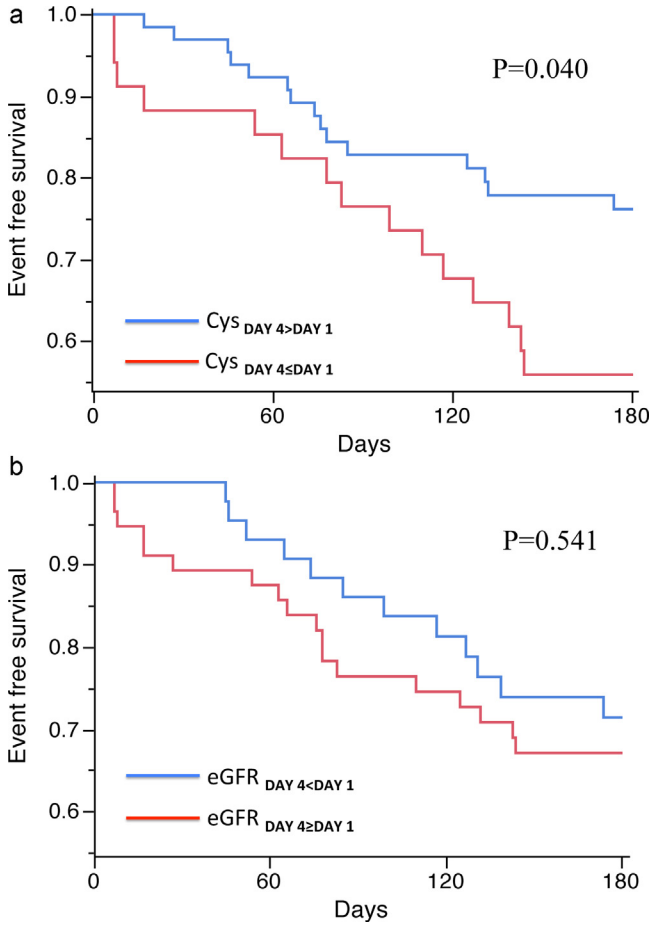

Fig. 3. (A) Event-free survival of patients with $Cys_{DAY\ 4\ >\ DAY\ 1}$ versus $Cys_{DAY\ 4\ \leq\ DAY\ 1}$. (B) Event-free survival of patients with $eGFR_{DAY\ 4\ <\ DAY\ 1}$ versus $eGFR_{DAY\ 4\ \geq\ DAY\ 1}$. Cys, cystatin C; eGFR, estimated glomerular filtration rate.

endpoints (Table 2). Neither the baseline nor the day 4 eGFR, BUN, and Cys-C serum concentrations were associated with death or re-hospitalization for ACD. Because there were only 30 events during the study period, we examined multiple variable regression analysis in several models of different number of covariates. High baseline sodium and an increase in Cys-C serum concentration between day 1 and day 4 were independent predictors of lower rates of death and re-hospitalization for ACD in all models nevertheless (Table 2). Moreover, after the addition of baseline Cys-C serum concentration to the multiple variable regression analysis, $Cys_{DAY\ 4\ >\ DAY\ 1}$ remained an independent predictor of primary study endpoint (HR 0.362; 95% CI 0.146–0.816; $p = 0.015$). We also constructed the multivariate model without Cys-C parameters but with renal parameters such as increase in creatinine or increase in BUN or decrease in eGFR, but no renal parameter was an independent predictor of primary study endpoint.

Discussion

In this study, fewer patients whose blood concentration of Cys-C increased during hospitalization for ACD died or were re-hospitalized for management of ACD over a 180-day follow-up than patients whose Cys-C did not increase. On the other hand, the long-term rate of death and re-hospitalization for management of ACD was similar in patients whose eGFR decreased or increased during the initial hospitalization for ACD. Renal function, whether at the time of hospitalization or at the time of discharge from the hospital, was not a predictor of long-term clinical outcome. These observations are in conflict with several recent studies, which reported that in-hospital WRF is a predictor of adverse clinical outcomes. Testani et al. found that aggressive fluid removal was strongly associated with WRF and a significant decrease in 180-day survival [8]. In the DOSE trial, a strategy of high-dose furosemide administration was associated with a more abundant diuresis and transient WRF, as well as improvements in some outcome measures [9]. Other recent studies have reported the association of hemoconcentration with WRF during treatment of ACD and favorable long-term prognosis [11–13]. In the EVEREST trial, hemoconcentration was associated with a higher incidence of in-hospital WRF, although renal function returned to baseline within 4 weeks after discharge of the patients from the hospital [13]. These observations support the hypothesis that WRF developing during treatment of ACD is caused by transient abnormalities in renal hemodynamics due to vigorous decongestion, vasodilation, or both. These studies also revealed a tendency for vigorous volume reduction during treatment of ACD to improve the long-term clinical outcomes. However, Metra et al. found that WRF in patients with signs of persistent congestion was explained by other pathophysiologic mechanisms than volume reduction alone and that, in these circumstances, WRF might be associated with adverse long-term clinical outcomes [14]. In this study, an increase in Cys-C, although not a decrease in eGFR, was associated with a lower long-term, event-free survival. This may reflect the properties of Cys-C, which can detect changes in GFR more reliably and rapidly than creatinine. So, recently a Japanese chronic kidney disease guideline recommended us to estimate GFR by Cys-C in addition to creatinine [15]. This might also mean that patients in the $Cys_{DAY\ 4\ >\ DAY\ 1}$ had undergone effective decongestion, and were generally responsive to treatment, which is concordant with their tendency to be less medicated with loop diuretics and to present with a preserved renal function at the time of hospitalization. Patients entering the hospital without a regimen of angiotensin-converting inhibitor or angiotensin receptor blocker can also develop in-hospital WRF, although respond favorably to the introduction of these medications during treatment of ACD.

The prognosis of patients who develop WRF or acute kidney injury during treatment of ACD varies depending on the threshold that has been adopted, as they can be divided between a group that responds to treatment of ACD and in whom the abnormalities of renal function are transient, versus a group refractory to treatment of ACD, in whom the hemodynamic impairment and fluid overload are major. In the latter group, the low cardiac output and high central and renal venous pressures may lower the glomerular filtration pressure and cause WRF. This may explain the higher incidence of atrial fibrillation, lower mean left ventricular ejection fraction, and higher heart rate at the time of hospitalization in patients presenting with $Cys_{DAY\ 4\ >\ DAY\ 1}$, whose cardiac output may be depressed and renal function worsened.

In patients with chronic or acute heart failure, a depressed renal function has generally been associated with a poor prognosis [28–30], an observation confirmed in studies using Cys-C [21,22]. In this study, the indices of renal function measured at the time of admission and discharge from the hospital did not predict the long-term prognosis, as observed in a few previous studies [10]. We believe that this is partly explained by changes from baseline, caused by ACD, in the indices of renal function. In some patients, renal function preserved during the chronic phase is depressed by transient congestion or low perfusion, while others, whose renal function is chronically impaired, recover a relatively better function by transient hemodilution during the hospitalization. Therefore, the measurements made at the time of hospitalization do not always reflect the true renal function [31]. We

Table 2
Non-adjusted and adjusted hazard ratios for all cause mortality and re-hospitalization up to 180 days.

	Unadjusted analysis			Adjusted analysis								
	HR	95% CI	p	Model 1			Model 2			Model 3		
				HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Baseline characteristics												
Age, per 10 years	1.142	0.828–1.716	0.453							1.058	0.716–1.660	0.792
Presence of:												
Female gender	1.031	0.497–2.118	0.969							1.254	0.587–2.673	0.555
Ischemic heart disease	1.521	0.732–3.123	0.256									
Atrial fibrillation	1.109	0.437–1.858	0.776									
Diabetes mellitus	0.933	0.419–1.949	0.858									
Hypertension	1.83	0.713–6.205	0.227									
Left ventricular ejection fraction, in 10% increments	0.972	0.786–1.207	0.801									
Body mass index, in 1 kg/m^2 increments	0.968	0.892–1.046	0.416									
Heart rate, in 10 bpm increments	0.883	0.710–1.070	0.214									
Blood pressure, in 10 mmHg increments												
Systolic	0.787	0.668–0.919	0.002	0.974	0.957–0.991	0.002	0.988	0.967–1.007	0.211	0.881	0.714–1.070	0.206
Diastolic	0.745	0.549–0.967	0.025									
Hemoglobin, in 1 g/dl increments	1.003	0.839–1.189	0.972									
Albumin, in 1 g/dl increments	1.281	0.567–2.942	0.555									
Blood urea nitrogen, in 10 mg/dl increments	0.904	0.633–1.235	0.543									
Estimated glomerular filtration rate, in 10 ml/min/1.73 m^2 increments	0.957	0.803–1.127	0.607									
Log cystatin C, in 1 unit increments	1.435	0.596–3.511	0.697									
Sodium, in 1 mEquiv./l increments	0.892	0.828–0.966	0.006	0.887	0.818–0.965	0.006	0.877	0.807–0.958	0.004	0.877	0.806–0.956	0.004
Potassium, in 1 mEquiv./l increments	0.446	0.244–0.824	0.01				0.501	0.228–1.133	0.096	0.498	0.224–1.143	0.099
Log bilirubin, in 1 unit increments	1.757	0.997–2.928	0.051				1.528	0.785–2.762	0.201	1.611	0.811–2.994	0.166
Log N-terminal pro B-type natriuretic peptide, in 1 unit increments	1.060	0.779–1.421	0.691									
Drug therapy on admission to the hospital												
Angiotensin-converting enzyme inhibitor or receptor blocker	1.803	0.872–3.922	0.113									
Beta-adrenergic blocker	1.422	0.690–2.934	0.336									
Diuretic	1.658	0.768–3.969	0.205									
Aldosterone blocker	1.174	0.491–2.536	0.700									
Drug therapy and variables measured during hospitalization												
Inotropes use	2.280	1.069–4.690	0.034				1.815	0.792–4.062	0.156	1.823	0.800–4.049	0.150
Increase in cystatin C between day 1 and day 4	0.481	0.233–0.991	0.047	0.470	0.228–0.971	0.042	0.426	0.199–0.900	0.026	0.415	0.193–0.885	0.023
Decrease in estimated glomerular filtration rate between day 1 and day 4	0.797	0.374–1.638	0.539									

believe, therefore that, besides the baseline measurements, the changes in renal function observed during treatment of ACD might more accurately reflect the patient's long-term prognosis. N-terminal pro B-type natriuretic peptide at the time of admission is also known to be a strong predictor of adverse outcome in ACD patients. In this study, high N-terminal pro B-type natriuretic peptide value at the time of admission tended to be associated with higher rate of primary endpoints but not significantly as in other small studies.

Limitations of the study

The association between increase in Cys-C and decreased rate of long-term adverse clinical events indicates a correlation between marker of WRF and favorable prognosis after ACD. This should promote the search for new markers in the urine or blood to detect true irreversible renal injury and correlate its occurrence with adverse prognosis. On the other hand, since Cys-C exerts various biological functions, it is possible that its changes reflect other pathologic processes, separate from eGFR, that influence the long-term prognosis [32,33]. Our study was also limited by the lack of direct measurements of GFR. If we would have systematically followed the renal function after discharge, in-hospital WRF may have been considered as a transient change with confirmation.

Conclusion

An increase in Cys-C serum concentration during hospitalization for management of ACD was associated with a decreased risk of death or re-hospitalization for ACD independently of the baseline renal function. This observation is consistent with recent studies, which found that in-hospital WRF based on measurements of creatinine was not associated with an adverse long-term prognosis.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no potential conflict of interest to disclose.

Acknowledgments

None.

References

[1] Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, et al. 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:1810–52.
[2] Authors/Task Force Members, McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GYH, Maggioni AP, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;14:1787–847.
[3] Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–39.
[4] Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis 2011;54:144–53.
[5] Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Cas LD. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail 2014;10:188–95.
[6] Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TDJ, Cleland JGF, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007;13:599–608.
[7] Klein L, Massie BM, Leimberger JD, O'Connor CM, Pina IL, Adams KF, Califf RM, Gheorghiade M, for the OPTIME-CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Circ Heart Fail 2008;1:25–33.
[8] Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–72.
[9] Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.
[10] Blair JEA, Pang PS, Schrier RW, Metra M, Traver B, Cook T, Campia U, Ambrosy A, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Konstam MA, et al. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. Eur Heart J 2011;32:2563–72.
[11] Van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol 2013;61:1973–81.
[12] Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. J Am Coll Cardiol 2013;62:516–24.
[13] Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, Maggioni AP, Nodari S, Konstam MA, Butler J, Filippatos G, EVEREST Trial Investigators. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail 2013;15:1401–11.
[14] Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54–62.
[15] Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease; 2012;p. 18–21 [in Japanese].
[16] Maisel AS, Katz N, Hillege HL, Shaw A, Zanco P, Bellomo R, Anand I, Anker SD, Aspromonte N, Bagshaw SM, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, et al. Biomarkers in kidney and heart disease. Nephrol Dial Transplant 2010;26:62–74.
[17] Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. Nephrol Dial Transplant 2014;29:1301–11.
[18] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.
[19] Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369:932–43.
[20] García Acuña JM, González-Babarro E, Grigorian Shamagian L, Peña-Gil C, Vidal Pérez R, López-Lago AM, Gutiérrez Feijóo M, González-Juanatey JR. Cystatin C provides more information than other renal function parameters for stratifying risk in patients with acute coronary syndrome. Rev Esp Cardiol 2009;62:510–9.
[21] Naruse H, Ishii J, Kawai T, Hattori K, Ishikawa M, Okumura M, Kan S, Nakano T, Matsui S, Nomura M, Hishida H, Ozaki Y. Cystatin C in acute heart failure without advanced renal impairment. Am J Med 2009;122:566–73.
[22] Dupont M, Wu Y, Hazen SL, Tang WH. Cystatin C identifies patients with stable chronic heart failure at increased risk for adverse cardiovascular events. Circ Heart Fail 2012;5:602–9.
[23] Pérez-Calvo JI, Ruiz-Ruiz FJ, Carrasco-Sánchez FJ, Morales-Rull JL, Manzano-Fernández S, Galisteo-Almeda L, Pascual-Figal D. Prognostic value of serum cystatin C and N-terminal pro B-type natriuretic peptide in patients with acute heart failure. Eur J Intern Med 2012;23:599–603.
[24] Lassus JPE, Nieminen MS, Peuhkurinen K, Pulkki K, Siirila-Waris K, Sund R, Harjola VP, for the FINN-AKVA Study Group. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J 2010;31:2791–8.
[25] Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams Jr KF, Dorobantu MI, Grinfeld L, Jondeau G, Marmor A, Masip J, et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program. J Am Coll Cardiol 2013;61:196–206.
[26] Tang WH, Dupont M, Hernandez AF, Voors AA, Hsu AP, Felker GM, Butler J, Metra M, Anker SD, Troughton RW, Gottlieb SS, McMurray JJ, Armstrong PW, Massie BM, Califf RM, et al. Comparative assessment of short-term adverse events in acute heart failure with cystatin C and other estimates of renal function: results from the ASCEND-HF trial. JACC Heart Fail 2015;3:40–9.
[27] JCS Joint Working Group. Guidelines for treatment of acute heart failure (JCS 2011). Circ J 2013;77:2157–201.
[28] Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure. J Am Coll Cardiol 2006;47:1987–96.
[29] Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422–30.
[30] Damman K, Valente M, Voors AA. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2013;35:455–69.
[31] Testani JM, McCauley BD, Chen J, Coca SG, Cappola TP, Kimmel SE. Clinical characteristics and outcomes of patients with improvement in renal function during the treatment of decompensated heart failure. J Card Fail 2011;17:993–1000.
[32] Manzano-Fernández S, Januzzi JL, Boronat-Garcia M, Bonaque-González JC, Truong QA, Pastor-Pérez FJ, Muñoz-Esparza C, Pastor P, Albaladejo-Otón MD, Casas T, Valdés M, Pascual-Figal DA. β-trace protein and cystatin C as predictors of long-term outcomes in patients with acute heart failure. J Am Coll Cardiol 2011;57:849–58.
[33] Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence? J Cardiol 2013;62:331–5.